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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
PORTNER, V	
ART UNIT	**PAPER NUMBER**
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DATE MAILED: 03/15/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/284,233	Meyer et al
Examiner	**Group Art Unit**
Portner	1645

☒ Responsive to communication(s) filed on *Dec 20, 2000*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-11 and 13-21* is/are pending in the application.

Of the above, claim(s) *16* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-11, 13-15, and 17-21* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-11 and 13-21* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim 12 has been canceled.

Claim 16 remains withdrawn from consideration

Claims 1-11, 13-16 and new claims 17-21 are pending.

Claims 1-11, 13-15 and 17-21 are under consideration.

Sequence Compliance

1. The instant Application is now in sequence compliance.

Specification

2. Please insert the following heading prior to the brief description of the figures on page 10, line 12. Brief Description of the Several Views of the Drawing(s): A reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74.

Rejections Withdrawn

3. Claims 1, 6, 12 and 13 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record in paper number 10, paragraph 11.

Rejections Maintained

4. Claims 1-12, 13-15 and 17-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production of recombinant DNA, vectors, host cells, chimeric proteins and antigenic compositions that comprise Helicobacter antigens the instant specification, does not reasonably provide enablement for preventive or therapeutic live vaccines that express any Helicobacter antigen, and compositions which comprise any nucleic acid sequence from Helicobacter as the active agent which is a mimeotope or immunogen that is encoded by a nucleic acid sequence that does not evidence original descriptive support. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for reasons of record in paper number 10, paragraphs 13 and 14.

5. Claims 1,2,5 and 10 rejected under 35 U.S.C. 102(b) as being anticipated by Evans et al (1993) for reasons of record in paper number 10, paragraph 16.

6. Claims 1-2, 5-6,7-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Odenbreit et al (April 1996) for reasons of record in paper number 10, paragraph 17.

7. Claims 1-2, 5, 10, 11, 13, 17-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Doidge (WO95/33482) in light of McKee (1992) for reasons of record in paper number 10, paragraph 18.

8. Claims 1,2,4,5, 10, 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Dore'-Davin et al (May 1996) for reasons of record in paper number 10, paragraph 19.

9. Claims 1-2,4-5,10-11, 13-15, 17-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Michetti (WO95/22987) for reasons of record in paper number 10, paragraph 20.

10. Claims 1-3,4-5,6-9,10-11,13-15, 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michetti (WO95/22987) in view of Russell et al (US Pat. 6,030,624) for reasons of record in paper number 10, paragraph 22.

11. Claims 1-4,7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell et al (US Pat. 6,030,624) in view of Bukanov et al (1994) for reasons of record in paper number 10, paragraph 23.

Response to Arguments

12. Applicant's arguments filed December 20, 2000 have been fully considered but they are not persuasive.

13. Applicant argues the rejection of claims 1-12, 13-15 and 17-21 under 35 U.S.C. 112, first paragraph (scope), by asserting the efficiency of Helicobacter (urease) proteins can be increased by expression from a heterologous live attenuated bacterium, and the live vaccine administered as an oral vaccine results in about 100% protection in a single dose.

14. In response, to the Arguments presented in pages 8-9 of Applicant's Amendment dated December 20, 2000, it is the position of the examiner that the arguments set forth are not commensurate in scope with the claimed invention. The independent claim is directed to the use of any attenuated microbial pathogen and is not limited to the presentation of urease immunogenic polypeptides or mimotopes in an attenuated Salmonella pathogen. Claim 1 may use any attenuated microbial pathogen, which would include viruses, and other attenuated bacterial pathogens and is not limited to urease, a known protective Helicobacter immunogen.

Immunogens are not by nature automatically protective as asserted by Applicant. Immunogens will induce an immune response, but the immune response need not be protective against infection and disease and useful in the treatment or prevention of Helicobacter infection. Immunogens can induce diagnostic immune responses that do not

eradicate infection; this is true of the long standing chronic infection caused by Helicobacter.

The scope of enablement rejection is maintained for reasons of record in paper number 10, paragraphs 13 and 14.

15. Applicant argues the rejection of claims 1,2,5 and 10 under 35 U.S.C. 102(b) as being anticipated by Evans et al (1993) by asserting that;

Evans et al "makes no mention of any medical applications of this protein, nor demonstrates that immunization with the adhesin subunit leads to the development of a protective immune response." and concludes

"Evans et al. clearly does not disclose the immunogenic recombinant attenuated microbial pathogen of the present invention."

16. In response to Applicant's assertion with respect to the application of Evans et al as anticipating the claimed compositions, it is the position of the examiner that Applicant's arguments are not commensurate in scope with the claimed invention of claims 1,2,5 and 10. Claim 2 is not limited just to Salmonella, but may be any type of entero-bacterial cell. Evans et al used E.coli, which is an entero-bacterial cell for the production of an attenuated microbial pathogen that expresses a heterologous Helicobacter immunogen.

The expressed Helicobacter antigen was immunostimulatory, immunoreactive and used to detect the adhesin binding sequences for host epithelial cells. An immune response, obtained

from immunization with the adhesin receptor sequence synthesized peptide, blocked hemagglutination of human erythrocytes by H.pylori (page 682, col. 2, paragraph 2), a type of protective immune response.

No evidence has been made of record to show that the immunogen of Evans is not able to induce a protective immunity. Inherently the compositions that comprises an attenuated microbial pathogen anticipates the now claimed invention. Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

17. The rejection of claims 1-2, 5-6,7-10 under 35 U.S.C. 102(b) as being anticipated by Odenbreit et al (April 1996) is argued;

"Odenbreit et al. makes no mention of medical applications of these truncated Helicobacter antigens, nor were any immunological studies performed" and asserts that "no indication that these antigens are capable of inducing a protective immune response." and further asserts that "[T]hese cells do not express a heterologous Helicobacter adhesin protein. Instead, these cells lack expression of the natural Helicobacter adhesin subunit, due to the transposon insertion within the gene.

18. Applicant's arguments filed with respect to Odenbreit have been fully considered but they are not persuasive because the claimed invention is not limited to an expressed protein, but may be any expressed Helicobacter polypeptide to include mimeotopes that are immunogenic. Contrary to Applicant's assertion that the polypeptides were not expressed, the transformed strain P1-140 expressed the adhesin polyeptide but at a very reduced level, approximately 10% of that of wild-type strains. (see page 366, col. 2, paragraph 2 and page 367 both columns at bottom of page). The open reading frames were determined to *correspond to* nucleic acid sequences that encode adherence proteins as shown through the disruption of bacterial binding to the corresponding receptors on eukaryotic cells. (See page 369, col. 2). The disclosed mutant strain of E.coli that encoded the heterologous nucleic acid sequence (plasmid used to produce clone P1-140) would be capable of causing the expression of the nucleic acid molecule in a target cell and anticipates the now claimed invention.

With respect to the assertion that the reference did not conduct any immunological studies, Applicant is referred to page 371, col. 1, paragraph 2, which discloses an immunological method used in obtaining information for the published paper.

The claimed compositions, that comprise a recombinant attenuated microbial pathogen that expresses a heterologous Helicobacter antigen, are disclosed by Odenbreit et al. The recombinant attenuated microbial pathogens inherently anticipate the now claimed compositions.

No evidence has been made of record to show that the composition of Odenbreit is not capable of being immunogenic. If applicants contend that this is not the case, applicants are

advised that the Office does not have the facilities for examining and comparing applicant's product with the prior art, and that the burden is on applicant to show a novel or unobvious difference between the claimed method and the method of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

19. The rejection of claims 1-2, 5, 10, 11,13, 17-21 under 35 U.S.C. 102(b) as being anticipated by Doidge (WO95/33482) in light of McKee (1992) is argued by asserting:

"Doidge et al. merely lists McGhee et al. as well as numerous other articles in a section entitled "References" and therefore "McKee et al. is improperly cited as part of this rejection.";

McKee is argued to teach the importance of a balanced Th1 and Th2 immune response but does not to provide how such an appropriate balance could be obtained for Helicobacter; and

"Doidge et al proposes that a recombinant Helicobacter live vaccine might be used for treatment of Helicobacter infections, no such evidence was presented."

20. Applicant's arguments filed with respect to Doidge have been fully considered but they are not persuasive because at page 8, line 19, the teachings of both Holmgren and McGhee are incorporated by reference, and not just listed in the References section as asserted by Applicant.

The claimed invention is not directed to a method of obtaining a balanced Th1 and Th2 immune responses, but is directed to recombinant attenuated bacterial pathogens that express

heterologous Helicobacter antigens for the induction of an immune response and the use of the attenuated microbial pathogen in a method of inducing an immune response.

The Doidge reference discloses and claims recombinant host cells that express a heterologous Helicobacter antigen, and in light of McGhee, the person of skill in the art would have known how to make and use the live recombinant microbial pathogens of Doidge. The reference also teaches the use of live viral vectors, as well as other live vaccine vectors that would express Helicobacter catalase in a method of inducing a protective immune response; formulation of these compositions for oral and parenteral administration to a host is taught (see all claims).

No evidence has been made of record to show that the composition of Doidge is not capable of being in immunogenic. If applicants contend that this is not the case, applicants are advised that the Office does not have the facilities for examining and comparing applicant's product with the prior art, and that the burden is on applicant to show a novel or unobvious difference between the claimed method and the method of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

21. The rejection of claims 1,2,4,5, 10, 17 under 35 U.S.C. 102(b) as being anticipated by Dore'-Davin et al (May 1996) is argued:

to "not disclose the use of any live vaccine";

"nor does Dore-Davin disclose any Helicobacter antigen capable of inducing protective immunity";

nor does the reference "contain any data indicating that the application of a live vaccine consisting of the recombinant bacteria expressing the Helicobacter antigen induces immunological protection in a host."

22. Applicant's arguments filed with respect to Dore'-Davin have been fully considered but they are not persuasive because the claimed invention is directed to recombinant attenuated microbial pathogens that express a Helicobacter heterologous immunogen, wherein the immunogen is capable of inducing a protective immune response. Applicant's arguments are directed to methods of treating and preventing infection, not the compositions of claims 1,2,4,5,10 and 17, and are therefore not commensurate in scope with the claimed inventions to which the Dore-Davin reference was applied. Dore-Davin clearly shows the production of a recombinant attenuated microbial pathogen that expresses an immunogen capable of inducing a protective immune response.

The immunogen of Dore-Davin is Helicobacter urease polypeptide, expressed by a recombinant attenuated microbial pathogen, and therefore meets the claimed invention. Any and all Helicobacter antigens need not be expressed simultaneously by the claimed recombinant attenuated microbial pathogen, only a single Helicobacter immunogen need be heterologous to the attenuated pathogen.

The rejection is maintained for reasons of record.

23. The rejection of claims 1-2,4-5,10-15 under 35 U.S.C. 102(b) as being anticipated by Michetti (WO95/22987) is asserted to:

disclose "only the use of purified, enzymatically inactive urease with cholera toxin as an adjuvant as a formulation for oral immunization"; and

Michetti et al is further asserted to not teach the use of an adjuvant that is "suitable for use in humans." and concludes

"Michetti et al. thus does not disclose the protective Helicobacter immunogen of the present invention.

24. Applicant's arguments filed with respect to Michetti have been fully considered but they are not persuasive because Applicant's arguments are not commensurate in scope with the claimed invention.

With respect to the type of heterologous Helicobacter immunogen contained in the attenuated microbial pathogen, it is the position of the examiner that the claimed invention is not limited to only those urease immunogens that are enzymatically active. Within the scope of the claimed invention are mimotopes of urease. These immunogens are not enzymatically active, though immunogenic. Therefore, arguments directed to the lack of enzymatic activity is not commensurate in scope with the claimed invention.

The claimed method is a method of treating a patient, the patient may be any type of patient and is not limited to humans, even if the methods were limited to humans, the reference

teaches the use of mucosal adjuvants and parenteral adjuvants, multiple modes of formulation of the compositions and the use of cholera toxin B subunit that has reduced toxicity.

With respect to Applicant's argument that states, "Michetti et al. thus does not disclose the protective Helicobacter immunogen of the present invention", it appears that Applicant is arguing the specific strain of Salmonella transformed with the specific plasmid used in the immunization of the instant Specification. This specific species of attenuated microbial pathogen is not recited in the claims. Applicant's argument is not commensurate in scope with the claimed invention.

25. The rejection of claims 1-11,13-15 and 17, 19-20 under 35 U.S.C. 103(a) as being unpatentable over Michetti (WO95/22987) in view of Russell et al (US Pat. 6,030,624) is argued:

"However, the cited references contain no suggestion or motivation for providing the immunological protection of the present invention."

"no teaching or suggestion is provided for a protective oral live vaccine consisting of an attenuated bacterial carrier that expresses a Helicobacter immunogen on its own (non-chimeric)"; and

the instant invention is able to "induce protective immunity of about 100% after a single dose application without use of additional adjuvants" and Russell uses cholera toxin A2/B as an adjuvant.

26. Applicant's arguments filed with respect to Michetti in view of Russell have been fully considered but they are not persuasive because applicant's arguments are not commensurate in scope with the claimed invention. The instant invention recites open language which permits the presence of other components in the compositions, such as adjuvants, and the methods would provide for the use of additional reagents and methods steps for the attainment of the desired immune response.

The phrase "*immunological protection of the present invention*", is being read to mean immunological protection against Helicobacter infection. Clearly Michetti in view of Russell teach, provide guidance and motivation for the construction of recombinant attenuated microbial pathogens, that comprise a recombinant AroA attenuated mutant Salmonella transformed to express a heterologous Helicobacter immunogen for the induction of a protective immune response directed against Helicobacter, a pathogen known to be associated with gastric ulcers. If an asserted meaning other than that read by the examiner for the quoted phrase above, the examiner would appreciate clarification of this argument relative to the claimed invention.

The claimed invention does not exclude the use of chimeric heterologous immunogens and therefore permits that inclusion of compositions that would encode more than one heterologous antigen.

Arguments directed to the wherein statement recited in claim 21, " wherein the composition is administered as a single dose" does not exclude the administration of

additional doses. Claim 21 defines the composition of claims 19 and 20 is administered as a single dose, but the method may comprise the administration of multiple doses because the claims recite "comprising language" and the methods could comprise additional administration steps.

The rejection over Michetti in view of Russell is maintained for reasons of record.

27. The rejection of claims 1-4,7-11 under 35 U.S.C. 103(a) as being unpatentable over Russell et al (US Pat. 6,030,624) in view of Bukanov et al (1994) is argued

to " provide no suggestion or motivation regarding the Helicobacter immunogen or live vaccine of the present invention."

"Russell et al. does not teach or suggest an attenuated pathogen comprising a Helicobacter immunogen that is capable of inducing protective immunity ";

the instant invention is " capable of inducing protective immunity of about 100% after a single dose application" and

"Bukanov et al fails to cure any of the deficiencies of Russell et al."

28. Applicant's arguments filed with respect to Russell in view of Bukanov have been fully considered but they are not persuasive.

The phrase "*immunological protection of the present invention*", is being read to mean immunological protection against Helicobacter infection. Clearly Russell suggests, teaches, and provides guidance for the construction of a recombinant attenuated microbial pathogens, that

comprise a recombinant AroA attenuated mutant Salmonella transformed to express a heterologous Helicobacter immunogen for the induction of a protective immune response directed against Helicobacter, a pathogen known to be associated with gastric ulcers (col. 9, lines 46 and 66).

Russell et al suggest the formulation of vaccine compositions for Helicobacter. Vaccine antigens induce protective immunity. Bukanov was cited for what the reference taught with respect to known Helicobacter antigens and their use in the production of recombinant attenuated microbial pathogens. Bukanov taught the person of ordinary skill that urease nucleic acid sequences were known and could be incorporated into a attenuated microbial pathogen for expression. At the time of filing of the instant Application, urease was known to be a protective Helicobacter antigen. The person of ordinary skill in the art at the time the invention was made would have been motivated to use a known protective Helicobacter immunogen in the formulation of a recombinant attenuated microbial pathogen for the induction of a protective immune response.

Arguments directed to the wherein statement recited in claim 21, " wherein the composition is administered as a single dose" does not exclude the administration of additional doses. Claim 21 defines the dose of claims 19 and 20 as a single dose, but the method may comprise the administration of multiple doses because the claims recite "comprising language" and the methods are not limited to only a single administration step. Applicant's arguments are not commensurate in scope with the claimed invention.

The rejection of Russell in view of Bukanov is maintained for reasons of record.

Conclusion

29. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

30. **Guy et al (US Pat. 6,126,938)** is cited to show methods of inducing a mucosal immune response through the administration of an expression system to a host.

31. **Malone et al (US Pat. 6,110,898)** is cited to show the administration of Helicobacter antigen encoding polynucleotide to a mammal for the induction of a mucosal immune response.

32. **Powell et al (US Pat. 5,877,159)** is cited to show a method of expressing a gene in a prokaryote using a eukaryote expression cassette, wherein an attenuated invasive bacterial is transformed, and Helicobacter pylori and Salmonella are claimed.

33. **Morrow et al (US Pat. 5,817,512)** is cited to show a recombinant polio virus (attenuated microbial pathogen) that comprises a nucleic acid sequence that encodes a protein from Helicobactor pylori or a fragment thereof (see claim 31).

34. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

35. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Vgp March 10, 2001

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